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Polycyclic N-Hetero Compounds. VII.[1] Reactions of Benzyl Ketones with Formamide XI

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On heating phenylacetone (III) with formamide in the presence of phosphoryl chloride (called the modified Vilsmeier reaction) afforded 4-methyl-5-phenylpyrimidine (IV), 5-phenyl-4-(5-pyrimidinyl)pyrimidine (V), and 3-methyl-2,4-diphenylaniline (VI). The modified Vilsmeier reaction of 3-methoxyphenylacetone (VII) gave 6-methoxy-3-methylisoquinoline (VIII), 4-β-formylaminovinyl-5-*m*-methoxyphenylpyrimidine (IX), 9-methoxybenzo[*f*]quinazoline (X), and 7-methoxybenzo[*f*]quinazoline (XI). The same reaction of 2-phenylcyclohexanone (XII) gave 8-phenyl-5,6,7,8-tetrahydroquinazoline (XIII) and 4-formylamino-4,4a,5,6,7,8-hexahydroquinazoline (XIV).

In the previous paper,[3] it was reported that the reaction of 3,4-dimethoxyphenylacetone (I) or 3,4-methylenedioxyphenylacetone (II) with formamide in the presence of phosphoryl chloride (called the modified Vilsmeier reaction) gave 3-methyl-6,7-dimethoxyisoquinoline or 3-methyl-6,7-methylenedioxyisoquinoline respectively. In order to investigate this isoquinoline cyclization for benzyl ketones, in the present paper phenylacetone (III), 3-methoxyphenylacetone (VII), and 2-phenylcyclohexanone (XII) were used as starting materials.

As shown in Chart 1, condensation of III under the modified Vilsmeier conditions gave 4-methyl-5-phenylpyrimidine (IV), 5-phenyl-4-(5-pyrimidinyl)pyrimidine (V), and 3-methyl-2,4-diphenylaniline (VI), but any isoquinoline derivative could not be isolated. It was already reported in our laboratory that the pyrimidine cyclization like the formation of IV was occurred in desoxybenzoin series,[4] but the cyclizations like V and VI have not been reported. Kato, *et al.*[5] reported that the Vilsmeier reaction, using dimethylformamide and phosphoryl chloride, of 4-methylpyrimidines gave pyrimidine-4-malonaldehyde derivatives. In our case, it was suggested that at first IV was formed and the further reaction occurred at the active 4-methyl group of IV to pyrimidinylpyrimidine (V). Thus, when the modified Vilsmeier reaction was carried out on IV, V was expectedly obtained more easily. This is a novel synthetic method of pyrimidinylpyrimidine. The presumed mechanism for the formation of VI is shown in Chart 2.

The modified Vilsmeier reaction of 3-methoxyphenylacetone (VII) gave 6-methoxy-3-methylisoquinoline (VIII) as main product, 4-β-formylaminovinyl-5-*m*-methoxyphenylpyrimidine (IX), 9-methoxybenzo[*f*]quinazoline (X), and 7-methoxybenzo[*f*]quinazoline (XI). Of these, VIII is the expected product, and IX is seemed to be an intermediate of pyrimidinylpyrimidine cyclization, that is, 5-*m*-methoxyphenyl-4-methylpyrimidine is formed at first, and it reacts furthermore with 2 moles of the modified Vilsmeier reagent to give IX, and under more vigorous conditions the side chain of IX will be cyclized to pyrimidine with the reagent.

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[1] Part VI: T. Koyama, T. Hirota, H. Hara, and S. Ohmori, *Chem. Pharm. Bull.* (Tokyo), **23**, 2015 (1975).

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[3] T. Koyama, M. Toda, T. Hirota, Y. Katsuse, and M. Yamato, *Yakugaku Zasshi*, **90**, 11 (1970).

[4] T. Koyama, Y. Katsuse, M. Toda, T. Hirota, and M. Yamato, *Yakugaku Zasshi*, **90**, 1207 (1970).

[5] T. Kato, H. Yamanaka, and H. Hiranuma, *Yakugaku Zasshi*, **90**, 870 (1970).

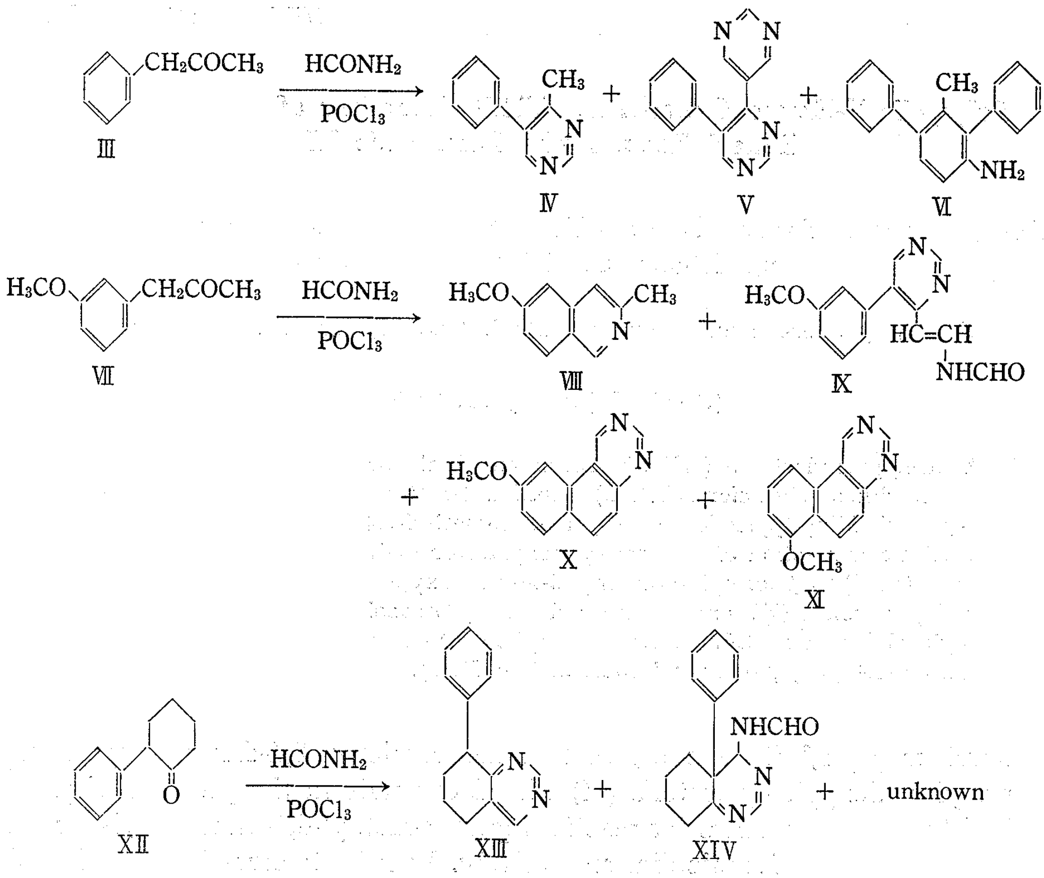

Chart 1

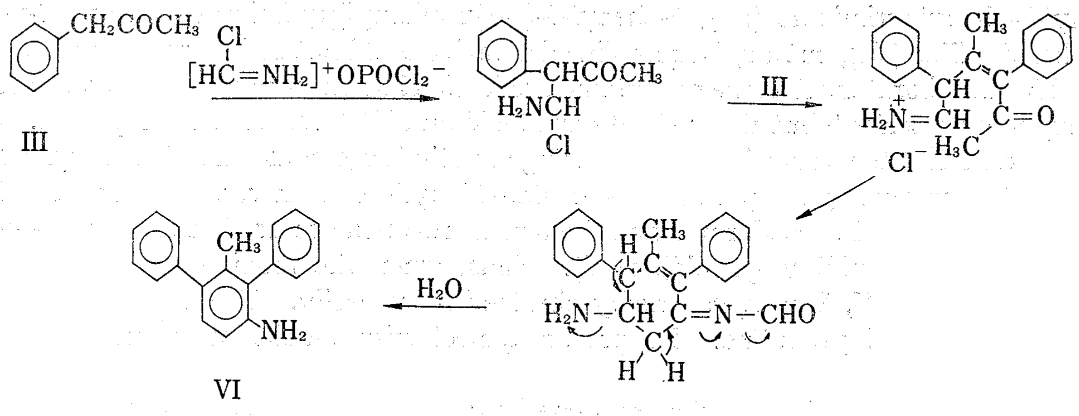

Chart 2

However, we did not try this cyclization because of very low yield of IX. X and XI are seemed to be electrophilic cyclization products of initially formed 5-*m*-methoxyphenyl-4-methylpyrimidine and 1 mole of the modified Vilsmeier reagent. The position of methoxyl group of X and XI was determined by the chemical shifts and coupling constants in nuclear magnetic resonance (NMR) (*cf.* experimental part).

Condensation of XII under the modified Vilsmeier conditions gave no isoquinoline, but quinazoline derivatives, that is, 8-phenyl-5,6,7,8-tetrahydroquinazoline (XIII), 4-formylamino-4a-phenyl-4,4a,5,6,7,8-hexahydroquinazoline (XIV), and unknown colorless plates, mp 227—228°, were isolated.

Experimental

Melting points are uncorrected. NMR spectra were taken on a Hitachi Model R-22 spectrometer (90 MHz) in $CDCl_3$ with tetramethylsilane as an internal standard (δ value), s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Infrared (IR) spectra were recorded on a Nihon Bunko Model IR-G spectrometer in KBr disk. UV spectra were taken on a Hitachi EPS-2 spectrophotometer in 99% EtOH. Mass spectra were taken on a Shimadzu LKB-9000 spectrometer with a direct inlet system.

The Modified Vilsmeier Reaction of Phenylacetone (III)——a) To 10 ml of $HCONH_2$, 6 ml of $POCl_3$ was added dropwise under stirring at room temperature keeping free from moisture. Regardless of exothermic and foamy reaction, the stirring was continued for another 1 hr. 1.5 g of III in 10 ml of dry toluene was added to this colloidal mixture under stirring. The mixture was heated gradually to 100° and stirred for 2.5 hr at that temperature. The reaction mixture was allowed to stand overnight at room temperature. After evaporation of excess $HCONH_2$ *in vacuo*, to the residue was added ice water. The solution was made alkaline with Na_2CO_3 and extracted with $(C_2H_5)_2O$, The $(C_2H_5)_2O$ layer was washed with H_2O, dried over anhydrous Na_2SO_4, and $(C_2H_5)_2O$ was evaporated. Benzene–cyclohexane (1 : 1)-soluble fraction of the residue was chromatographed over alumina. The first benzene eluate was fractionated with preparative thin-layer chromatography (TLC) on silica gel (benzene: $(C_2H_5)_2O = 1 : 2$). The fraction of *Rf* value *ca.* 0.6—0.7 was collected and recrystallized from petr. ether to give 250 mg (13%) of 4-methyl-5-phenylpyrimidine (IV) as colorless needles, mp 76—76.5°. *Anal.* Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.90; H, 5.78; N, 16.44. NMR: 2.45 (3H, s, CH_3), 7.39 (5H, m, C_6H_5), 8.42 (1H, s, pyrimidine ring C-6-H), 8.93 (1H, s, pyrimidine ring C-2-H).

The second benzene eluate was fractionated with preparative TLC on silica gel (benzene: $(C_2H_5)_2O = 5 : 7$). The fraction of *Rf* value *ca.* 0.5 was collected and recrystallized from C_2H_5OH to give 46 mg (2.5%) of 5-phenyl-4-(5-pyrimidinyl)pyrimidine (V) as pale yellow needles, mp 99°. *Anal.* Calcd. for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 72.01; H, 4.45; N, 23.68. Mass Spectrum: *m/e* $(M^+) = 234$. NMR ($CDCl_3$): 7.10—7.55 (5H, m, C_6H_5), 8.78 (3H, s, pyrimidine ring C-6, C-4′, C-6′-H), 9.13, 9.30 (each 1H, s, pyrimidine ring C-2, C-2′-H). NMR (CF_3COOD): 7.35—7.78 (5H, m, C_6H_5), 9.39 (1H, s, pyrimidine ring C-6-H), 9.55 (2H, s, pyrimidine ring C-4′, C-6′-H), 9.77, 9.85 (each 1H, s, C-2, C-2′-H). UV λ_{max}^{EtOH} mμ (ε): 212 (18800), 252 (9800), 275 (7200).

b) To 40 ml of $HCONH_2$, 24 ml of $POCl_3$ was added dropwise under stirring at room temperature keeping free from atomospheric moisture. The stirring was continued for another 1 hr under the exothermic and foamy reaction. To the colloidal mixture, 6.0 g of III in 40 ml of $HCONH_2$ was added at once. After the vigorous exothermic and foamy reaction was over, the mixture was heated at 100—110° for 2 hr and allowed to stand overnight at room temperature. After addition of ice water to the reaction mixture, the solution was made alkaline with Na_2CO_3 and extracted with benzene. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and benzene was evaporated. 1) Hot cyclohexane-soluble fractions of the residue were combined (refluxed with three 50 ml of cyclohexane). After evaporation of cyclohexane, the brown solid was recrystallized from C_2H_5OH to give 1.05 g of V (10.3%) as pale yellow needles, mp 99°, identical with the material prepared from the method (a). 2) Hot cyclohexane-insoluble residue was chromatographed over alumina with benzene. The benzene–$(C_2H_5)_2O$ (1 : 1) eluate was fractionated with the preparative TLC on silica gel (benzene: cyclohexane = 19 : 1). The fraction of *Rf* value *ca.* 0.5 was collected and recrystallized from petro. ether to give 150 mg (1.5%) of 3-methyl-2,4-diphenylaniline (VI) as colorless needles, mp 110—111°. *Anal.* Calcd. for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.33; H, 6.71; N, 5.40. Mass Spectrum: *m/e* $(M^+) = 259$. IR ν_{max}^{KBr} cm^{-1}: 3430, 3340 (N–H). NMR: 1.85 (3H, s, CH_3), 3.40 (2H, b, NH_2, D_2O exchange), 6.70, 7.08 (each 1H, ABq, C-5, C-6-H), 7.35 (10H, m, 2-C_6H_5). Although IV was not isolated, it was confirmed by TLC.

The Modified Vilsmeier Reaction of IV——To 10 ml of $HCONH_2$, 6 ml of $POCl_3$ was added dropwise under stirring at room temperature keeping free from atomospheric moisture. After 1 hr stirring, 2.2 g of IV in 30 ml of $HCONH_2$ was added dropwise to the colloidal mixture. After the exothermic and foamy reaction was over, the mixture was heated gradually to 100°, stirred for additional 3 hr at that temperature, and allowed to stand overnight at room temperature. After addition of ice water to the reaction mixture, the solution was made alkaline with Na_2CO_3 and extracted with benzene–$(C_2H_5)_2O$ (1 : 1). The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was dissolved in as little CH_2Cl_2 as possible and chromatographed over alumina with benzene. The benzene–CH_2Cl_2 (9 : 1) eluate was recrystallized from C_2H_5OH to give 560 mg (18.5%) of V as pale yellow needles, mp 99°, identical with the specimen prepared from the method (a).

The Modified Vilsmeier Reaction of 3-Methoxyphenylacetone (VII)——To 10 ml of $HCONH_2$, 6 ml of $POCl_3$ was added dropwise under stirring at room temperature keeping free from atomospheric moisture. After 0.5 hr stirring, 2 g of VII in 10 ml of $HCONH_2$ was added dropwise to the colloidal mixture. After addition was completed, the mixture was stirred at room temperature for 1 hr then at 80° additional 5 hr. After addition of ice water to the reaction mixture, the solution was made alkaline with Na_2CO_3 and extracted with $(C_2H_5)_2O$ followed by $CHCl_3$. Each organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and the solvents were evaporated independently. After sublimation of the $(C_2H_5)_2O$ extract *in vacuo*, the sublimate was recrystallized from dil. C_2H_5OH to give 110 mg (5.5%) of 6-methoxy-3-methylisoquinoline (VIII) as colorless feathers, mp 115—116°. *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.40; H, 6.39; N, 8.04. Mass Spectrum: *m/e* $(M^+)=173$. NMR: 2.62 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 6.93 (1H, d, $J=2.5$ Hz, C-5-H), 7.18 (1H, dd, $J=8.5$ Hz, $J=2.5$ Hz, C-7-H), 7.44 (1H, s, C-4-H), 7.82 (1H, d, $J=8.5$ Hz, C-8-H), 9.01 (1H, s, C-1-H). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 231 (4.90), 302 (3.72), 315 (3.48).

The above residue of sublimation and the $CHCl_3$ extract were combined and chromatographed over alumina. The $CHCl_3$ and C_2H_5OH eluates were fractionated with preparative TLC on silica gel (benzene–$(C_2H_5)_2O$ $=1:4$) independently. The fraction of *Rf* value *ca.* 0.6 was collected and recrystallized from petro. ether to give 20 mg (0.8%) of 7-methoxybenzo[*f*]quinazoline (XI) as colorless needles, mp 133—135°. *Anal.* Calcd. for $C_{13}H_{10}ON_2$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.43; H, 4.62; N, 13.10. Mass Spectrum: *m/e* $(M^+)=210$. NMR: 4.05 (3H, s, OCH_3), 7.15 (1H, bd, $J=8$ Hz, C-8-H), 7.74 (1H, bt, $J=8$ Hz, C-9-H), 7.93 (1H, d, $J=9$ Hz, C-6-H), 8.31 (1H, bd, $J=8$ Hz, C-10-H), 8.68 (1H, d, $J=9$ Hz, C-5-H), 9.42 (1H, s, C-3-H), 10.08 (1H, s, C-1-H). The fraction of *Rf* value *ca.* 0.5 was collected and recrystallized from petro. ether to give 36 mg (1.5%) of 9-methoxybenzo[*f*]quinazoline (X) as colorless needles, mp 153°. *Anal.* Calcd. for $C_{13}H_{10}ON_2$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.31; H, 4.80; N, 13.20. Mass Spectrum: *m/e* $(M^+)=210$. NMR: 4.05 (3H, s, OCH_3), 7.40 (1H, dd, $J=8$ Hz, $J=2.5$ Hz, C-8-H), 7.78 (1H, d, $J=9$ Hz, C-6-H), 7.91 (1H, d, $J=8$ Hz, C-7-H), 8.10 (1H, bs, C-10-H), 8.15 (1H, d, $J=9$ Hz, C-5-H), 9.46 (1H, s, C-3-H), 10.09 (1H, s, C-1-H). The fraction of *Rf* value *ca.* 0.3 was collected. Although the structure (IX) was suggested by its NMR and mass spectra data, it could not be confirmed because of its small amount. Mass Spectrum: *m/e* $(M^+)=255$. NMR: 3.85 (3H, s, OCH_3), 5.79 (1H, bd, CH=), 7.0 (3H, m, phenyl C-2′, C-4′, C-6′-H), 7.46 (2H, m, N–CH=, phenyl C-5′-H), 8.48 (1H, bd, $J=6$ Hz, CHO, changed to singlet with D_2O exchange), 8.65 (1H, s, pyrimidine C-6-H), 9.15 (1H, s, pyrimidine C-2-H). The signal of NH was unobserved.

The Modified Vilsmeier Reaction of 2-Phenylcyclohexanone (XII)——To 25 ml of $HCONH_2$, 14 ml of $POCl_3$ was added dropwise under stirring and cooling. After addition was completed, the mixture was stirred for another 1 hr and then 5.22 g of XII in 25 ml of $HCONH_2$ was added dropwise to the reaction mixture at room temperature. The mixture was heated gradually to 80° and stirring was continued for additional 7.5 hr at that temperature. After allowing to stand overnight at room temperature, to the reaction mixture was added ice water. The solution was made alkaline with aq. ammonia and extracted with $(C_2H_5)_2O$ followed by $CHCl_3$. The organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, and the solvents were evaporated independently. The crystalline residue of $(C_2H_5)_2O$ extract was recrystallized from C_2H_5OH to give 250 mg (3.3%) of 4-formylamino-4a-phenyl-4,4a,5,6,7,8-hexahydroquinazoline (XIV) as colorless plates, mp 252—254°. *Anal.* Calcd. for $C_{15}H_{17}ON_3$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.33; H, 6.76; N, 16.56. Mass Spectrum: *m/e* $(M^+)=255$. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3360, 3160 (N-H), 1673 (C=O). NMR (Me_2SO-d_6): 1.82, 2.35 (each 4H, m, 4-CH_2), 4.95 (1H, bd, $J=9$-Hz, C-4-H), 6.89 (1H, bs, CHO), 7.34 (5H, m, C_6H_5), 8.16 (1H, bs C-2-H), 8.39 (1H, b, NH, D_2O exchange), it seemed that higher field shift of the signal C-4-H or CHO was resulted from the anisotropic effect of the C-4a-phenyl group.

The residue of recrystallization of $(C_2H_5)_2O$ extract and the $CHCl_3$ extract were combined and chromatographed over alumina with benzene. Elution of benzene–$CH_2Cl_2=3:1$ gave 1.05 g (16.7%) of 8-phenyl-5,6,7,8-tetrahydroquinazoline (XIII) as viscous oil, which was purified by formation of picrate. The picrate was recrystallized from C_2H_5OH, mp 173—175°. *Anal.* Calcd. for $C_{20}H_{17}O_7N_5$: C, 54.67; H, 3.90; N, 15.94. Found: C, 54.54; H, 3.76; N, 15.72. NMR of the free base (XIII): 1.75—2.45 (4H, m, C-6, C-7-H), 2.84 (2H, bt, $J=6$ Hz, C-5-H), 4.21 (1H, bt, $J=7$ Hz, C-8-H), 6.98—7.50 (5H, m, C_6H_5), 8.53 (1H, s, C-4-H), 8.97 (1H, s, C-2-H).

Elution of benzene–C_2H_5OH (9: 1) gave 44 mg of unknown colorless plates, 227—228°.

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